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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
08/485,943	06/07/95	FRIEDMAN	J 600-1-087-CI

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HM12/0829

EXAMINER

YUCEL, I

ART UNIT	PAPER NUMBER
1636	33

DATE MAILED: 08/29/00

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.
08/485,943

Applicant(s)
Friedman et al.

Examiner
Remy Yucel

Group Art Unit
1636



☒ Responsive to communication(s) filed on May 8, 2000

☐ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire three month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) 124, 132-137, 139-143, 145-153, 155-160, and 163-173 is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) 124, 132-137, 139-143, 145-153, 155-160, and 163-173 is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been
☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). 3, 30 & 3

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

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DETAILED ACTION

Claims 124, 132-137, 139-143, 145-153, 155-160 and 163-173 are pending in the application. This Office action is in response to the amendment filed 21 June 2000.

Continued Prosecution Application

The request filed on 21 June 2000 for a Continued Prosecution Application (CPA) under 37 CFR 1.53(d) based on parent Application No. 08/485,943 is acceptable and a CPA has been established. An action on the CPA follows.

Information Disclosure Statement

The information disclosure statement filed 13 August 1999 appears to be a substantial duplicate of the statement filed 08 May 2000 which contains additional references. Accordingly, only the PTO-1449 from the latter IDS has been initialed by the Examiner (to avoid processing of duplicate references by the printer in the event the application is allowed).

Claim Objections

Claims 150-153 and 160 are objected to because they depend from canceled claims.

Response to Amendment

Claims 124, 132-137, 139-143, 145-153, 155-160 and 163-173 stand rejected under 35 U.S.C. 112, first paragraph for the reasons set forth in the Office actions mailed 21 May 1998 (paper 17) and 06 April 1999 (paper 22), scope of enablement.

The rejection of claims 133, 141, 147 and 157 under 35 U.S.C. 112, first paragraph, written description has been withdrawn in light of Applicant's remarks found at page 24.

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The rejection of claim 164 stands rejected under 35 U.S.C. 112, second paragraph has been withdrawn in light of Applicant's remarks found at page 24.

Response to Arguments

From page 17 to the middle of page 19, Applicant argues that the specification enables methods which modify the body weight of a mammal. Applicant repeats portions of previous Office actions which establish that administration of the **leptin protein or expression of the leptin gene only to *ob/ob* mice results in the modulation of weight**. Applicant takes issue with the position that because the specification does not teach how to identify individuals with the specific genetic background which benefits from leptin administration or expression of the leptin gene (*ob/ob*), it would take undue experimentation to identify such individuals and therefore the specification is not enabling (see bottom of page 17).

At page 18, Applicant points to the alleged diagnostic methods provided by the specification found at pages 65-69 of the specification as teachings that guide the skilled artisan in determining the individuals discussed immediately above. This argument has been considered, but is not found persuasive. This passage is merely a generalized description of how antibodies are used in different types of assays and fails to provide specific details and protocols which would enable the skilled artisan to specifically identify *ob/ob* individuals, for example, humans (that are not mice from a known, bred, strain). In fact, as will be discussed below, the field still does not know how to identify individuals that are likely to benefit.

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Next, Applicant states that he is puzzled as to why it would take undue experimentation to determine individuals within a population given the teachings of Maffei *et al.* (published after Applicant's filing date). This argument has been considered, but is not found persuasive. A careful reading of Maffei *et al.* reveals that their methods do not result in the linkage of the human *OB* gene to an obese phenotype (see the middle of the second column on page 679), thus their methods do not "diagnose" the specific subset of individuals. In fact, these teachings further corroborate the position of the Examiner, since "mutations in the coding sequences of *OB* are not a common cause of obesity in humans." (see discussion at page 681).

At page 20-23, Applicant indicates several references which allegedly illustrate enablement of the instant methods. These references and their relevance to the issues at hand will be discussed.

Applicant contends that the teachings of the Farooqi *et al.* reference show that the claimed invention was enabled. The first observation to be made is that this reference was published some four years after Applicant's filing date, during which time the authors of the paper identified a **specific mutation** associated with early-onset obesity. Using this marker, the authors of the instant reference were able to identify an individual that was homozygous for the mutation. Secondly, Farooqi *et al.* administered recombinantly-produced leptin **protein**, they did not administer expression vectors comprising the leptin coding region. Clearly, the specification is completely silent with respect to the mutation used by Farooqi *et al.* Secondly, the instant claims are drawn to gene therapy, not protein therapy as exemplified by Farooqi *et al.* This distinction is

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not a trivial one and its importance will be discussed below. It appears that the teachings of the instant reference does not really illustrate the enablement of the instant invention.

Next, Applicant discusses the study conducted by Heymsfield *et al.* (10/1999). The first observation is that, like Farooqi *et al.*, Heymsfield *et al.* used protein therapy. Thus, the relevance of this teaching to rejections regarding the enablement of gene therapy claims is not clear.

Secondly, in the conclusion found at page 1568, the authors of the study call for more research into the **potential** role for leptin and related hormones in the treatment of human obesity. This indicates that the field, even as of 1999, recognized leptin alone or in combination with other hormones as a treatment. Further, at page 1573 (see second paragraph from the bottom of column 1), Heymsfield *et al.* teach “the therapeutic potential of rL [recombinant leptin] to treat obesity cannot be determined from this study.”

Applicant then cites the teachings of Fletcher *et al.* (1995, 1996) and Muzzin *et al.* corroborate what was already known, that the *ob/ob* mouse genetic background responds to leptin. The showings in these reference are not commensurate with the scope of the claims and do not illustrate enablement for the full scope of the instant claims.

Applicant's next set of references allegedly show that gene therapy in general is enabled and has been used successfully. It is not clear what relevance the quotation from Albelda *et al.* has, since the instant invention is for the gene therapy of obesity, not lung diseases. Secondly, the future tense used by the authors clearly indicates that as of April 2000, gene therapy was not regarded as a tool in use at the time of the invention or even today. At the summary found at

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page 657, Albelda *et al.* teach that “the field of gene therapy is still in its infancy.....it is highly likely that in the **near future**, gene therapy will be shown to have clear efficacy in treatment of such diseases as hemophilia and in the stimulation of angiogenesis in peripheral vascular disease and myocardial ischemia.” They teach that although none of the diseases in their study was cured, valuable lessons were learned in their trials, especially in defining the challenges of relatively inefficient and transient delivery of transgene *in vivo*.” Clearly, the authors recognize many challenges must be met before gene therapy is considered efficacious and predictable, these points will be further discussed below.

Applicant cites the Romano *et al.* reference to show how many trials have been registered. The relevance of the number of trials on the enablement of gene therapy to modulate weight is not clear. However, a close reading of the reference, for example the latter part of the abstract illustrates that the authors do not recognize the effectiveness of current gene therapy programs. They also cite the growing concern of safety of gene delivery, they conclude, “despite the latest significant achievements reported in vector design, **it is not possible to predict to what extent gene therapeutic interventions will be effective in patients and what time frame.**” At page 31, they teach that vector design must address very difficult tasks, including transduction efficiency and safety precautions and that the current degree of vector development is still not sufficiently adequate to meet all the requirements for phase III (efficacy) trials.

Next, Applicant cites Cavazzana-Calvo *et al.* as evidence that gene therapy provides clinical benefit against SCID-X1. Again, the relevance of the teachings of this paper, the *ex vivo*

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therapy of an immunodeficiency disease, to the issues at hand regarding the modulation of weight through *in vivo* gene therapy methods, is not completely clear. There is nothing in this reference which suggests that the claimed methods are enabled. The same observation is applicable to the Heslop and Manno *et al.* references. Heslop focuses on ex vivo therapy protocols for diseases with completely different etiologies than obesity. She also teaches that gene therapy protocols suffer from a number of obstacles including vector design. From her conclusion at page 192, it is clear that she anticipates that gene therapy should work in the future for leukemia.

Thus, contrary, to Applicant's assertion, the references above fail to illustrate that (these) gene therapy regimens have had sustained clinical effect in the subjects (since none of the papers clearly demonstrates either a clinical effect or one that is sustained). The scientific community, which includes those at the USPTO accepts the **potential** of gene therapy as a practical approach in the future when more of the obstacles to safe and efficacious gene delivery are removed, as a viable treatment. The discussion above clearly indicates that in none of the references cited by Applicant, have the authors recognized an efficacious gene therapy protocol.

Applicant concludes by citing patents drawn to gene therapy issued by the Office. Every application is judged on its own merits and because neither the Examiner nor Applicant is privy to the prosecution histories of these patents, this point becomes a non-issue.

The following is a further discussion as to the unpredictability of gene therapy and an analysis of the Forman factors applicable.

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The nature of the invention. Methods of targeting nucleic acids into host cells *in vivo* and subsequent expression fall into the broad area known as gene therapy methods. Several obstacles are recognized for gene therapy methods because successful therapy methods are not only predicated on the ability of successful delivery, but also on sufficient levels of exogenous gene expression as well as sufficient duration of expression.

The state of the prior art and the predictability or unpredictability of the art. The following references are cited herein to illustrate the state of the art of gene therapy as recently as 2000. Marshall reports that there are still difficulties in getting genes transferred efficiently to target cells (pg. 1054 last column, second paragraph) and that the field of gene therapy needs “a lot of basic research of vectors and cell biology” before gene therapies can be qualified as successes (pg. 1055). Crystal (cited by Applicant) describes the “ideal gene transfer vector” which has among its attributes, ability to efficiently transfer genes and be specific for its target. He further states that the ideal vector is conceptually impractical since the applications for human therapies are broad and it is likely that the vector will likely be different for each application (pg. 409, center column).

The inability to target viral vectors effectively is just but one hurdle facing gene therapy. A second major obstacle is to ensure delivery of genes in sufficiently high numbers to target cells to be effective when administered *in vivo*. Both Marshall and Crystal also cite the delivery of genes to adequate numbers of target cells and/or ensuring sufficient gene expression in those cells as major difficulties for gene therapy methods (pg. 1050, top of center column, pg. 1054, last

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column, second paragraph and pg. 409, center column, respectively). Orkin *et al.* state that the low efficiency of gene transfer and the consistency of achieving long term expression of transferred genes are still obstacles of potential gene therapy strategies. While long term gene expression can be demonstrated for a few instances in mouse experiments, in human trials, the extent of gene expression is uncertain (it is noted that this reference is dated some 6 months after Applicant's filing date).

A further difficulty is the unpredictable nature of gene therapy when one tries to extrapolate from animal models to human systems. Marshall reports that there have been no unambiguous evidence that genetic treatment methods have produced therapeutic benefits and that only hints of benefits have appeared despite the sizeable number of clinical trials for different diseases (pg. 1050, first column, pg. 1054, center column). Crystal also presents a long list of clinical trials that have yet to yield therapeutic benefits, "no human disease has been cured by human gene transfer and it is not clear when this will be accomplished" (pg. 407, first column). Crystal further states that "Humans are not simply large mice. There have been several surprise examples, in which predictions from gene transfer studies in experimental animals have not been borne out in human safety and efficacy trials." (pg. 409, first column). Orkin *et al.* further state that while animal models are valuable for the design of gene therapy approaches, these models, such as mouse models do not faithfully mimic relevant human conditions, thus the relevance of animal models to human disease is not certain in most instances. Further, "confidence in current approaches to somatic gene therapy would arise if a genuine deficiency in an animal were

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unequivocally corrected. Although genetic defects in animals have been corrected by introducing transgenes into the germline, somatic gene transfer has not permanently corrected a genetic disease in an animal” (see pages 8-11). Further, Orkin reports that “efficacy has not been established for any gene therapy protocol.” (page 13).

Verma *et al.* teach problems skilled artisans face in the art of *in vivo* gene delivery or transfer and affirms the findings of Orkin *et al.* While the long term goals of the field remain the same, that is clinically efficacious therapy protocols, the art as a whole recognizes that fundamental problems must be solved, the infrastructure, if you will, must be established before the development of efficacious therapy protocols can take place. These articles illustrate and support the above articles in the assertions that the art of *in vivo* gene therapy is still in its infancy despite an enormous body of work by highly skilled artisans. The cited references also show that the art is highly unpredictable and that the art recognizes a number of fundamental stumbling blocks to gene transfer. At column three on page 239, Verma *et al.* state that “[t]he Achilles heel of gene therapy is gene delivery...” As discussed above, this is also the same hurdle that faces any gene transfer protocol. It also illustrates that in the two years between the Orkin report and the Verma *et al.* reference, that the situation remains the same despite another two years of vast experimentation .

William French Anderson, another noted researcher in the field of gene therapy also teaches that there is no conclusive evidence that a gene-therapy protocol has been successful in the treatment of a human disease (see top of page 25, first column). At page 26, second column,

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he teaches that despite steady progress, long-term, stable, appropriate level gene expression *in vivo* in a range of cell types is still to be accomplished, once this is achieved, then the hurdle of regulated gene expression must be addressed.

Fox describes problems with viral vectors, including adenoviral vectors for delivery in terms of safety, gene expression and targeting. He cites problems associated with high vector doses, and the fine line between doses which result in toxicity and doses which are potentially therapeutic. These teachings further illustrate the unpredictable nature of gene therapy.

Kafri *et al.*, Gura *et al.* and Yanovski *et al.* are cited to illustrate further problems associated specifically with leptin gene therapy. Kafri *et al.* teach that (gutless, replication defective) adenoviral vectors comprising the coding region of the OB gene induce cellular immune responses against transduced (infected) cells which has a negative impact on long-term expression of the gene of interest, in this case, the coding region for leptin. Kafri *et al.* conclusion section clearly indicates the highly unpredictable nature of gene therapy protocols-- for example it is not predictable that one can avoid CTL responses because some infected cells are not recognized since the basis for this is as yet unknown. Kafri *et al.* teach that the levels of "inoculum" for therapy protocols have sufficient levels of viral proteins, even though the vectors themselves do not contain sequences encoding viral sequences, to trigger an immune response. They conclude that for sustained production of the foreign protein (which is the scenario required for the instant claims) or for readministration of the foreign gene, adenoviral vectors still face a formidable challenge.

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Gura teaches that even leptin protein therapy has questions of efficacy. Gura reports that only a few individuals responded to leptin treatment, "it's looking very much as if there is no real effect except in a subset of patients." (see second page). Gura then reports that Heymsfield's team (see discussion above) now plans to try to identify exactly what factors made the subset of people more responsive to leptin, indicating that at the time of the invention, this was not known, as well as methods for identifying the patient population were also not known, contrary to Applicant's assertions. "If successful, says Heymsfield, one could screen people beforehand for certain markers and then know the probability of responding would be much higher." These teachings indicate the importance of being able to identify the subset of patients in which leptin has a chance of working.

Finally, Yanovski *et al.* review the advances in basic obesity research. They too teach that in a very narrow subset of obese animals, specifically *ob/ob* mice, injections of the leptin protein complements the low levels of circulating leptin in these mice. Based on the findings that the vast majority of obese individuals appear to have normal sequences for leptin and its receptor and have high levels of circulating leptin, they suggest that leptin's primary function is not to protect against obesity, but as a signal for inadequate energy intake. Thus, there is significant reasons to believe that leptin treatment will not be efficacious in the vast majority of cases of obesity.

While these references acknowledge the usefulness of gene therapy and the possibility of developing efficacious strategies in the future, they also illustrate that there are numerous obstacles to successful gene therapy which current methods still must overcome. As such, the

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disclosed utilities of the present specification which are drawn to gene therapy methods are credible. The present rejection, therefore is not for lack of utility, but rather for lack of enablement for methods other than those limited to *in vitro* methods.

The amount of direction or guidance presented in the specification and the presence or absence of working examples. Applicants have not provided guidance in the specification toward specific gene transfer protocols which would avoid the technical obstacles recognized in the art, as described above.

The specification fails to teach the *in vivo* delivery and expression of an *OB* coding region, let alone modulation of weight through the introduction of a nucleic acid construct into a mammal.

The breadth of the claims. The breath of the claims is very broad. They are drawn to *in vivo* methods of delivery, expression and modulation of weight using any expression vector comprising coding regions which in turn, comprise various amino acid substitutions.

The quantity of experimentation. The references cited above describe a sizeable number of studies, with only hints of therapeutic benefits--because of the significant obstacles to gene delivery or transfer. Despite the tremendous amount of experimentation already devoted to developing gene transfer methods, significant barriers still exist even after Applicants' filing date. This indicates that thus far, no amount of experimentation has resulted in a clearly successful and/or **predictable** gene transfer and therapy method. For example, the importance of being able to identify the subset of individuals which respond to additional leptin has already been established

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above. If the skilled artisan was not able to prescreen for these individuals and then attempted the claimed methods and obtained negative results, how would the skilled artisan interpret the results to make modifications for subsequent attempts? Are the negative results the result of inappropriate genetic background of the individuals being treated? Are the negative results due to inefficient gene transfer such that not enough cells have the leptin coding region? Are the results due to insufficient gene expression? The specification does not teach what levels of gene expression is necessary, so the skilled artisan would need to empirically determine this. Are the negative results due to adequate expression levels, but not an adequate duration of time? Each of these possibilities would need to be explored and determined by the skilled artisan, THEN, the skilled artisan would need to devise appropriate solutions to remedy the problem--which as discussed above, the art has yet to resolve even 5 years after Applicant's filing date. Clearly, this level of experimentation would be undue on the part of the skilled artisan.

It has been established that a patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion. Tossing out the mere germ of an idea does not constitute enabling disclosure. While every aspect of a generic claim certainly need not have been carried out by an inventor, or exemplified in the specification, **reasonable detail must be provided in order to enable the skilled artisan to understand and carry out the invention.** It is true that a specification need not disclose what is well known in the art. That general, oft-repeated statement is merely a rule of supplementation, not a substitute for a basic enabling disclosure. It means that the omission of minor details does not cause a specification to

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fail to meet the enablement requirement. However, in light of the above discussion, it has been established that there is very little in the art of gene transfer that is well known and predictable.

To attempt to practice the claimed invention one of skill in the art would turn to the specification for guidance in practicing the invention. As set forth above, however, the specification lacks sufficient guidance to surmount the technical difficulties recognized in the art. Another source of guidance for one skilled in the art, the prior art, again for reasons set forth above, also lacks solutions to overcome the considerable list of obstacles recognized in the field of gene therapy.

In the absence of instruction from the specification and the prior art, one of skill in the art would resort to trial and error or empirical experimentation to navigate the obstacles and practice the claimed invention. Again, as established above, solutions to these technical problems have been elusive despite an enormous amount of experimentation due to a number of factors, including the unpredictable nature of the art of gene transfer and therapy. Such unpredictability would warrant even more experimentation, with no true expectation of a measure of success. Therefore, the amount of experimentation required to practice the claimed invention would be undue on the part of one skilled in the art.

Conclusion

Certain papers related to this application may be submitted to Art Unit 1636 by facsimile transmission. The faxing of such papers must conform with the notices published in the Official

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Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 CFR § 1.6 (d)). The Group 1600 FAX numbers are (703) 308-4242 or (703) 305-3014. Unofficial faxes may be sent to the examiner at (703) 305-7939. NOTE: If applicant *does* submit a paper by fax, the original signed copy should be retained by Applicant or Applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Remy Yucel, Ph. D. whose telephone number is (703) 305-1998. The examiner can normally be reached on Monday through Fridays from 8:30 am to 5:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. George Elliott can be reached at (703) 308-4003.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.



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August 28, 2000